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Cannabis, psychosis and schizophrenia: unravelling a complex interaction

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ABSTRACT

The relationship between cannabis and psychosis and schizophrenia has tested the field of addiction for decades, and in some ways serves as measure of our ability to provide a credible contribution to public health. As cannabis is used widely, many people are interested in the risks the drug poses to mental health. This paper focuses upon a seminal study examining this, the trajectory of subsequent research findings and what this has meant for understanding and communicating risk factor information. These studies provided evidence of a dose–response relationship between cannabis and psychosis, and that for those individuals with schizophrenia cannabis exacerbated their symptoms. The findings fit with a multi-causal model in which vulnerability interacts with a precipitating agent to produce a disease outcome. Even though this is a common model in epidemiology, it has proved difficult to communicate it in this case. This may be because at a population level the increased risk is weak and the vulnerabilities relatively rare. It may also be because people bring strongly held preconceptions to interpreting a complex multi-causal phenomenon.

Q3 **Keywords** Andréasson, cannabis, Hall, psychosis, schizophrenia.

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INTRODUCTION

Drug use and mental health are connected, but we still have a limited understanding of what exactly the relationship is and why, for some individuals, their mental health is compromised by their drug use while for others there appears to be no adverse effect. The role of cannabis in psychosis and schizophrenia demonstrates neatly the complexity of the challenge of investigating cause and effect, and the wider social and political factors that influence the way that knowledge on this issue has developed. This paper explores research and opinion on this issue that developed in the late 1960s through to the millennium.

It is worth stating that the idea that cannabis might be problematic for mental health is not a recent preoccupation. In 1772, Grose [1] describes the problems he witnessed as a result of bang (cannabis) in India: '...it is hard to say what pleasure can be found in the use of it, being very disagreeable to the taste, and violent in its operation, which produces a temporary madness, that in some, when designedly taken for that purpose, ends in running what they call a-muck, furiously killing everyone they meet, without distinction, until themselves are knocked on the head, like mad dogs'.

Although the relationship between cannabis and psychosis has received attention for more than 100 years, it was only when its use became more popular in many countries during the 1960s and 1970s that there was a serious interest in the role it might have in acute psychosis and schizophrenia as a chronic disease.

Setting the scene

The 1960s saw a rapid increase in the use of mood-altering drugs such as cannabis in many western countries. In the United Kingdom, the influential Wootton report in 1969 [2] used H. M. Customs and Excise conviction data as its proxy for cannabis use to show a huge increase in convictions for cannabis offences in the late 1960s. The Wootton report described the literature as 'vast and contradictory', and made a number of recommendations for the future direction of research, including to 'investigate possible cases of cannabis psychosis and, in particular, to study the concomitant effect of other drugs and of the abuse of alcohol in these cases'.

Then, as today, information and policy decisions about cannabis were influenced by preconceptions, but there were also familiar-sounding methodological problems. In a review of the evidence in relation to cannabis and psychosis, Schofield [3] concluded that '…few of the reports are specific about the dose and type of cannabis. It is a bit like assuming beer and methylated spirits are equally damaging'.

However, some researchers were concerned about the mental health problems associated with increasing cannabis use in the population, so the 1970s saw renewed attention paid to the connection.

Researchers, mainly from the United States, investigated how exposure to cannabis might have a role in psychosis [4–8]. These were mainly small case studies using convenience sampling. The exception was a large cohort study (n = 36 000) of American soldiers based in Germany which, unfortunately, was unable to distinguish between concurrent use of alcohol, tobacco and cannabis in those participants who developed psychosis [9].

Collectively, these studies began to try to cast light on the relationship between cannabis and psychosis, and in particular the direction of the relationship. Spencer [4] captured neatly one of the conundrums which would persist for decades: was cannabis responsible for a short-lived acute psychotic reaction, or was it a trigger for the longer-lasting problem of schizophrenia? This was not an easy question to answer, as cannabis use may occur in the prodromal period of acute psychosis prior to a diagnosis of schizophrenia.

1980s

This decade also witnessed the advent of community mental health care, in which large institutions were decommissioned and patients moved into their local communities. This exposed these former patients to substances to which they had had limited access previously.

The classic paper that I wish to highlight here is the Swedish conscript study led by Andréasson *et al.* [10]. The authors were ambitious in trying to establish the causal role of cannabis in schizophrenia and take account of confounding variables.

A constellation of events triggered Sven Andréasson's interest in this issue. Andréasson observed that cannabis was used widely in Sweden at the time, and he had also heard reports from psychiatrists who were concerned about the use of cannabis by their patients who had psychosis. They had noticed that these patients were returning to hospital and that their psychoses had deteriorated following discharge, rather than improving. At the same time, Andréasson's supervisor, Peter Allebeck, mentioned a registry that had sat in a basement for 15 years and was about to be destroyed. Surprised that no one had looked at this rich source of data, they thought it would be a good idea to see what it revealed about the relationship between cannabis and psychosis.

The authors used this military conscript registry to analyse data from two questionnaires that were given to a cohort of 45 570 Swedish men at the point of their conscription between 1969 and 1970. Seven per cent of this cohort refused to answer questions relating to drug use and were excluded from the study. Clearly, this 7% could have altered the results significantly if they refused to participate due to fear of disclosing cannabis use. However, 4290 (9.4%) of the conscripts confirmed that they had used cannabis on at least one occasion prior to their conscription into the army. Andréasson was keen to explore level of exposure to cannabis and any consequent diagnosis of schizophrenia. He and his co-authors distinguished between infrequent and frequent use. Frequent use was defined as using cannabis on 50 or more occasions, a cut-off inherited from research into smoking cigarettes at the time. Although level of exposure had been explored previously it had not been investigated in a cohort of this size. By exploring two levels of exposure to cannabis among the conscripts, Andréasson was able to show that there was a dose–response relationship between cannabis use and schizophrenia. This was an important finding, and helped to direct future research which confirmed this association [11].

Unlike previous studies, the study by Andréasson and colleagues tried to control for potential confounders such as alcohol, tobacco and psychiatric diagnosis at the point of conscription. Their stratified analysis showed that an elevated risk of schizophrenia remained after controlling for such confounders. They reported and recognized the significance of the relationship between a psychiatric diagnosis at the point of conscription in 1969/70 and developing schizophrenia at the point of follow-up in 1983.

The study found that the relative risk of developing schizophrenia increased with greater use of cannabis. However, they were careful to point out that of the 274 conscripts who had a diagnosis of schizophrenia at follow-up only 21 were frequent users of cannabis. This led them to discuss the possibility that cannabis use might be caused by an emerging schizophrenia in the individual; in other words, schizophrenia precedes cannabis use. This vexed tangle continues to be studied and debated today.

The authors made an additional important contribution when they referred to the stress vulnerability model of Zubin & Spring [12]. They applied this model to suggest that problems such as schizophrenia can lie dormant until a person is exposed to a trigger such as a psychoactive drug, which then produces the symptoms of psychosis or schizophrenia. Andréasson thought that their findings pointed to cannabis as such a trigger in a small

vulnerable group of their male sample; so although Andréasson alerted us to this dynamic interaction among biology, psychology and environment in the 1980s, we have yet to apply this intelligence to people with psychosis who use cannabis [13].

Andréasson advanced our understanding by highlighting two distinct components of the relationship among cannabis, psychosis and schizophrenia. First, it was possible that cannabis could trigger psychosis in a vulnerable group of people who would not otherwise have had this toxic reaction. Andréasson remembers that this was a particularly contentious part of the conclusions of the original study. Secondly, exposure to cannabis elevated the risk of developing schizophrenia in a dose-dependent fashion.

It is important to note that the concept of a distinct cannabis psychosis was contested throughout this decade by those who viewed it as a constructed disease influenced by race and culture, a view promoted by members of the medical profession who were not attending to environmental factors [14]. Some psychiatrists did not find the term 'cannabis psychosis' useful, and even those who did could not agree on what it meant [15].

Consequently, we leave the 1980s with evidence for an association between cannabis and psychosis, but its nature was still unclear. Although the Swedish conscript study found an elevated risk of schizophrenia, Andréasson concluded that: 'A statistical association between cannabis consumption and schizophrenia does not necessarily imply a causal association. Cannabis consumption might, on the contrary, be caused by an emerging schizophrenia'. To this day, Andréasson believes that these findings are valid, although he is even more sceptical about the observational studies and the role of confounding factors, particularly other drugs to which participants have been exposed.

Nonetheless, this study provided clues about a connection between cannabis and schizophrenia that helped to set the direction of future research but was insufficient to offer credible advice to individuals or to inform populations via public health.

1990s

Doubt about the term 'cannabis psychosis' and the association between cannabis and psychosis continued with a review by Thornicroft [16], who decided that there was insufficient epidemiological evidence to warrant a distinct diagnosis of cannabis psychosis.

Irrespective of whether a distinct diagnosis could be justified, researchers continued to consider whether cannabis use preceded psychosis or if it was the symptoms of psychosis that led to cannabis use [17]. This revealed the many confounding factors that interact over time, which still make this type of inquiry challenging.

Adding to the problem of confounders was the issue of how cannabis consumption and potency had been measured in studies to this point. Thomas rightly alerted us to the difficulty of comparisons between study groups [18], a problem that persists to this day with no universally agreed method for how such variables should be assessed and reported in research.

In parallel, there was further debate about causation of psychosis and the role that cannabis might play. In the 1990s international classification indexes DSM and ICD both recognized cannabis psychosis as a distinct diagnostic category, but the evidence to support the diagnosis and criteria was being debated. Gruber & Pope reviewed the literature and surveyed more than 9000 psychiatric admissions, concluding that there was no convincing evidence to support the syndrome [19]. The current iterations of DSM and ICD continue to classify cannabis psychosis, but offer more detailed subcategories that recognize the various ways in which these two factors might relate to each other. For example, the DSM now recognizes that cannabis withdrawal is a consideration.

In 1998, Wayne Hall published a seminal review, 'Cannabis use and psychosis', which offered an analysis of the two dominant hypotheses providing an insight into collective knowledge up to this point in time [20]. The first hypothesis he reviewed was that heavy cannabis use causes a specific cannabis psychosis, a theory that had prevailed since the early 1970s and continues to be unresolved up to this point. The second hypothesis was that cannabis use precipitated schizophrenia, or at least makes the symptoms worse.

Reflecting the scepticism of some in the previous decade, Hall was not convinced by the idea of a distinct cannabis psychosis. His forensic examination of the evidence up to the time of his review points to poorly defined features of such a phenomenon with too wide a range of clinical features. A lack of controlled studies also leaves the case appearing weak.

For the second hypothesis, Hall found that the quality of evidence was richer, but interpretation was not straightforward. Hall pointed out rightly that finding a person with schizophrenia who has only used cannabis was rare, as most will also have used alcohol. Alcohol use mattered as it, too, has been associated with severe mental health problems such as psychosis [21].

I want to offer here a small but important discussion about the role of self-medication. Hall, in my view, rightly normalized the reasons for substance use by people with schizophrenia. Their reasons are exactly the same as those who do not have schizophrenia: to relieve boredom, to provide stimulation, to feel good and to socialize. Although this aspect has received little attention since Hall's review, these points have been replicated [22]. Having very ordinary reasons for using drugs not only helps us to

empathize, but is an important reminder not to pathologize behaviour. The emphasis Hall gives this is as valid today as it was 20 years ago.

Hall also discussed how cannabinoids increase dopamine release, and showed that excessive dopamine can produce psychotic symptoms. However, the dopamine theory has since been challenged, along with the role cannabinoids play [23,24].

As with Andréasson, Hall pointed to the stress vulnerability model to help explain why cannabis use could precipitate schizophrenia without supporting the idea that cannabis played a simple causal role. Rather, he argued that there is a complex interplay between genetics, environment and stress vulnerability.

Hall made the case for the lack of evidence supporting a causal role for cannabis in schizophrenia by examining the epidemiological data. While cannabis use increased at a population level in the 1970s and 1980s there was no associated increase in the incidence of schizophrenia. However, limitations in the incidence rate data for psychosis and schizophrenia have been highlighted [24]. One study in London found that between 1965 and 1999 the incidence of schizophrenia had doubled, and that those who used cannabis were overly represented in this group [25].

CONCLUSIONS

We ended the last century with some clear advice based on the efforts of researchers during the previous three decades: namely, that for those individuals who already have schizophrenia cannabis use can exacerbate symptoms. Similarly, both Andréasson and Hall drew our attention to the importance of the stress vulnerability model, which emphasizes the interplay between genes, environment and stress vulnerability in motivating people to use cannabis prior to these same individuals developing schizophrenia.

Demonstrating the way in which knowledge accumulates, Andréasson was aware of the importance of a dose–response relationship between cannabis and psychosis, but his research was the first to demonstrate this in a large observational study. This helped to set the focus and direction of research on this issue during the following decades.

Declaration of interests

None.

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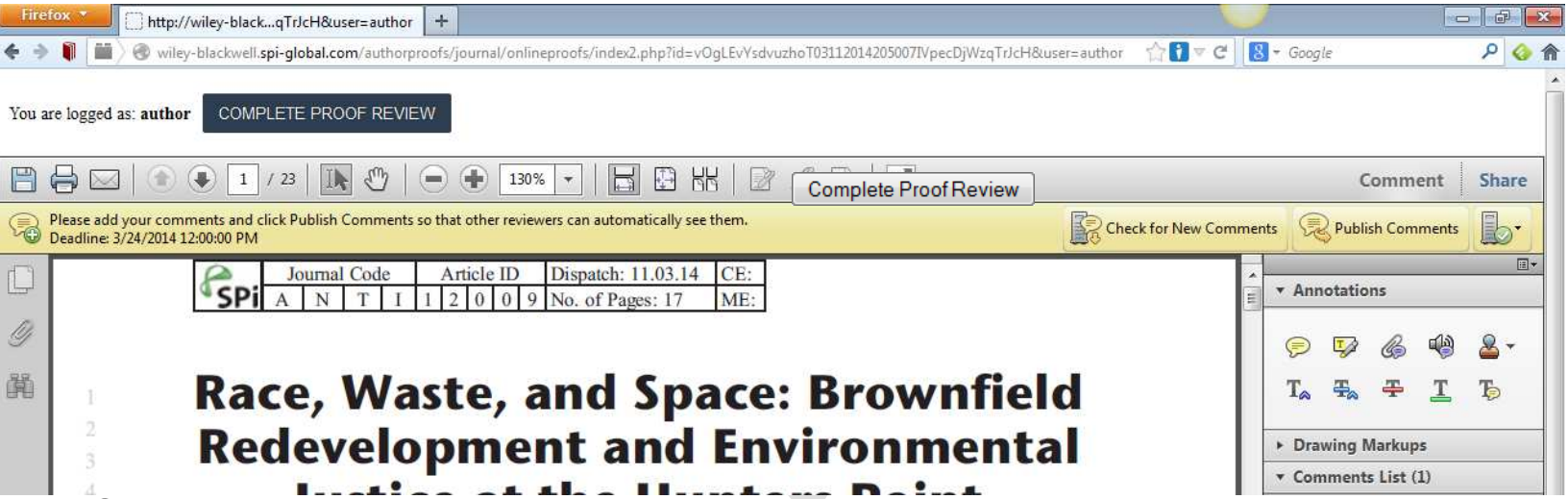

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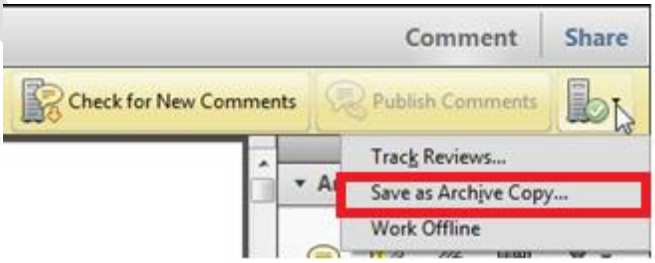

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